BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2012.04445.x

Commentary

Incident diabetes and statins: the blemish of an undisputed heavy weight champion?

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. . . All that glisters is not gold . . .
–William Shakespeare, Merchant of Venice, Act 2, Scene 7

In the aftermath of multiple clinical trials involving thousands of participants, statins or 3-hydroxy-methlyglutaryl coenzyme A (HMG-CoA) reductase inhibitors, have arguably emerged as the undisputed heavy weight champions of therapeutic strategies for the modulation of cholesterol concentrations and inflammation for primary and secondary prevention of atherosclerotic cardiovascular (CV) events, including stroke [1–4]. Alas, to all good pharmacologic interventions the well-known phrase '. . . all that glisters is not gold . . .' may be quite applicable here, as attendant collateral damage (side effects) may reduce the usefulness of these agents which currently fill our arsenals in disease warfare. Here-to-fore, myalgia, myopathy, rhabdomyolysis and derangement of liver enzyme levels have been traditional concerns associated with the use of statins, until we became aware of the arrival of new-onset diabetes at the scene in the wake of burgeoning pharmacoepidemiological evidence. The link between statin therapy and diabetes was first heralded by a *post hoc* analysis of the West of Scotland Coronary Prevention Study (WOSCOPS) [5], with a claim of beneficial effects of pravastatin on incident diabetes, and later re-ignited by the finding of increased incident diabetes with rosuvastatin treatment in Justification for the Use of Statins in Primary Prevention: an intervention Trial Evaluating Rosuvastatin (JUPITER) [6]. There now exists a body of evidence to support the notion that statins are diabetogenic, culminating in the recent action by the United States (US) Food and Drug Administration (FDA) to include the risk of hyperglycaemia and development of type II diabetes in the safety label of statins.

In this edition of the British Journal of Clinical Pharmacology, Zaharan and colleagues present evidence in support of the diabetogenicity of statins [7]. In their retrospective study, which employed the platform of the Irish Health Service Executive Primary Care Reimbursement Services (HSE-PCRS) national pharmacy claims database, they analyzed 239 628 individuals on statin therapy and a control group of 996 043 during a 7 year period. They report that the use of statins is associated with an increased risk of new onset diabetes (adjusted HR = 1.2, 95% CI 1.17, 1.23) [7].This association was consistent across types of statins and increased with the duration of use and cumulative dose. However, these findings were primarily driven by rosuvastatin (adjusted HR = 1.42, 95% CI 1.33, 1.52), atorvastatin (adjusted HR = 1.25, 95% CI 1.21, 1.28) and simvastatin (HR = 1.14, 95% CI 1.06, 1.23). Furthermore, the authors employed restricted cubic spline functions to provide insight on the shape or form of the relationship between incident diabetes and the duration of use and dose of statins. In this context, the association between duration of statin use and incident diabetes was linear for simvastatin, atorvastatin and rosuvastatin, while the risk associated with dose was linear for simvastatin, but non-linear for the other two.

It is important to remark that the lack of statistical significance for the association between fluvastatin and incident diabetes (adjusted HR = 1.04, 95% CI 0.91, 1.18) may be due to the much smaller sample of participants in the group (n = 3125). However, the same reason is not tenable for the non-significant results noted for pravastatin (n = 41 899, adjusted HR = 1.02, 95% CI 0.98, 1.06). Indeed, pravastatin may be different as suggested by previous reports of improved insulin sensitivity associated with its use [8]. On this point, there is an observation that is worthy of note. The US FDA drug safety communication did not differentiate between statins, but interestingly there has been a delay or lack of enforcement of the safety label changes for pravastatin, which perhaps reflects the possibility that pravastatin may indeed differ from other statins per dose-dependent risk of incident diabetes. On a different note, the authors acknowledge that the increased risk of incident diabetes was also noted in association with other

lipid modifying agents such as ezetimibe and fibrates, and thus entertained the possibility of confounding by indication.

Even though the report by Zaharan *et al*. [7] is consistent with other reports of incident diabetes during extended use of statins, many questions remain unanswered. The associations with cumulative dose and with duration of exposure provide biological plausibility, but the potential mechanisms underlying these findings are incompletely understood. Furthermore, we are not clear about the implication these findings have for the use of statins, a class of medications remarkably effective for modulating cholesterol concentrations and inflammation, and a bulwark in the prevention of atherosclerotic CV disease. In this context, there are questions as to whether there are patient characteristics that confer increased risk for incident diabetes during statin therapy, and how to approach the universal quest of balancing risks *vs.* benefits.

The diabetogenic effects of statins may centre on altered islet beta cell insulin secretion via the convergence of multiple mechanisms that compromise the integrity and function of the beta cells and thus precipitate dysregulation of glucose metabolism. Experimental and pathological evidence supports a paradigm that implicates the inhibition of beta cell glucose transporters, delayed ATP production, pro-inflammatory and oxidative intracellular effects of plasma-derived cholesterol, inhibition of calcium channel-dependent insulin secretion and beta cell apoptosis. The integration of these processes is captured by Figure 1, which provides a framework for how statins may effect the development of diabetes. The proposed mechanisms in the illustrated paradigm have been discussed in detail in a recent review [9]. Notably, if pravastatin is indeed different as speculated above, then the underlying mechanism for statin-induced diabetes may bear little or no relevance to HMG-CoA synthase inhibition but to alterations in cholesterol composition of cell membranes, and thus question the beta islet centred model of statin-induced dysglycaemia.

The efficacy of statins for primary and secondary prevention of CV events is well established even at low (<2mmol l^{-1}) LDL-cholesterol concentrations [10], and among diabetics, regardless of type of diabetes, lipid profile and baseline characteristics [11, 12]. However, the absolute risk of developing diabetes during statin use is very small, one case per 1000 patient-years of treatment [13]. To put this in context, 255 (95% CI 150, 852) patients have to be treated for 4 years before a statin-induced case of incident diabetes occurs [13]. However, a composite of nine vascular events (death, myocardial infarction, stroke and coronary revascularization) would be avoided by treating 255 patients for the same duration. This clearly outweighs the risk of incident diabetes (9:1 benefit *vs.* risk ratio). Thus, the small but potential risk of incident diabetes does not obviate the relevance of statins for CV risk reduction. Rather, in the absence of clear biochemical or clinical predictors for the occurrence of incident diabetes during extended statin use we need to do our best to tailor statin therapy based on the balance between risks *vs.* benefits in each patient. In this context, it may suffice to primarily employ traditional lifestyle modification in low CV risk populations where the benefits may not offset the associated risk of new-onset diabetes. In addition, age appears to be a characteristic worthy of note when considering statin therapy. In the meta-analysis by Sattar and colleagues age was the only patient baseline characteristic that was a predictor of incident diabetes [13], as the case in the current report by Zaharan *et al*., where the significant association between statin use and incident diabetes was primarily driven by the elderly participants [7]. These consistent findings should encourage caution with elderly patients, particularly those with low CV risk profile.

Statin therapy has led to remarkable reduction in CV endpoints at the relatively small but potential consequence of new-onset diabetes. However, statins are not the only medications that have been linked to increased incidence of diabetes. Indeed, they share this characteristic along with atypical antipsychotics, β-adrenoceptor blockers, thiazide diuretics and niacin, all of which remain in use due to their favourable benefit : risk ratio. As of yet, we do not know whether statin-induced diabetes is reversible akin to statin-induced cognitive deficits, which are reversed upon cessation of therapy as clearly documented in the US FDA expanded safety label statement. If statin-induced diabetes were reversible, it would have implications for the nature of its underlying mechanisms, and therefore should constitute an important focus for future research. Of note, if withdrawal of statin therapy reverses statin-induced diabetes, it would not represent an optimal option for patients with moderate to high CV risk, in whom there is no question or adjudication as to whether the benefits of statin therapy outweigh the risk of dysregulation of glucose metabolism. As a general approach, careful monitoring of blood sugar during treatment with statins is reasonable, and elderly patients may require careful attention. Furthermore, since the jury is still out on the underlying mechanisms for the diabetogenic effects of statins, the need for biochemical and clinical predictors of incident diabetes represents an area for further research, which may help refine our approach to patient selection and management. Along these lines, it is important to evaluate potential gene polymorphisms that may underpin statin-related diabetes, similar to the established association between the SLCO1B1 gene variant rs4149056 and myopathy with simvastatin [14], which now guides patient care.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf

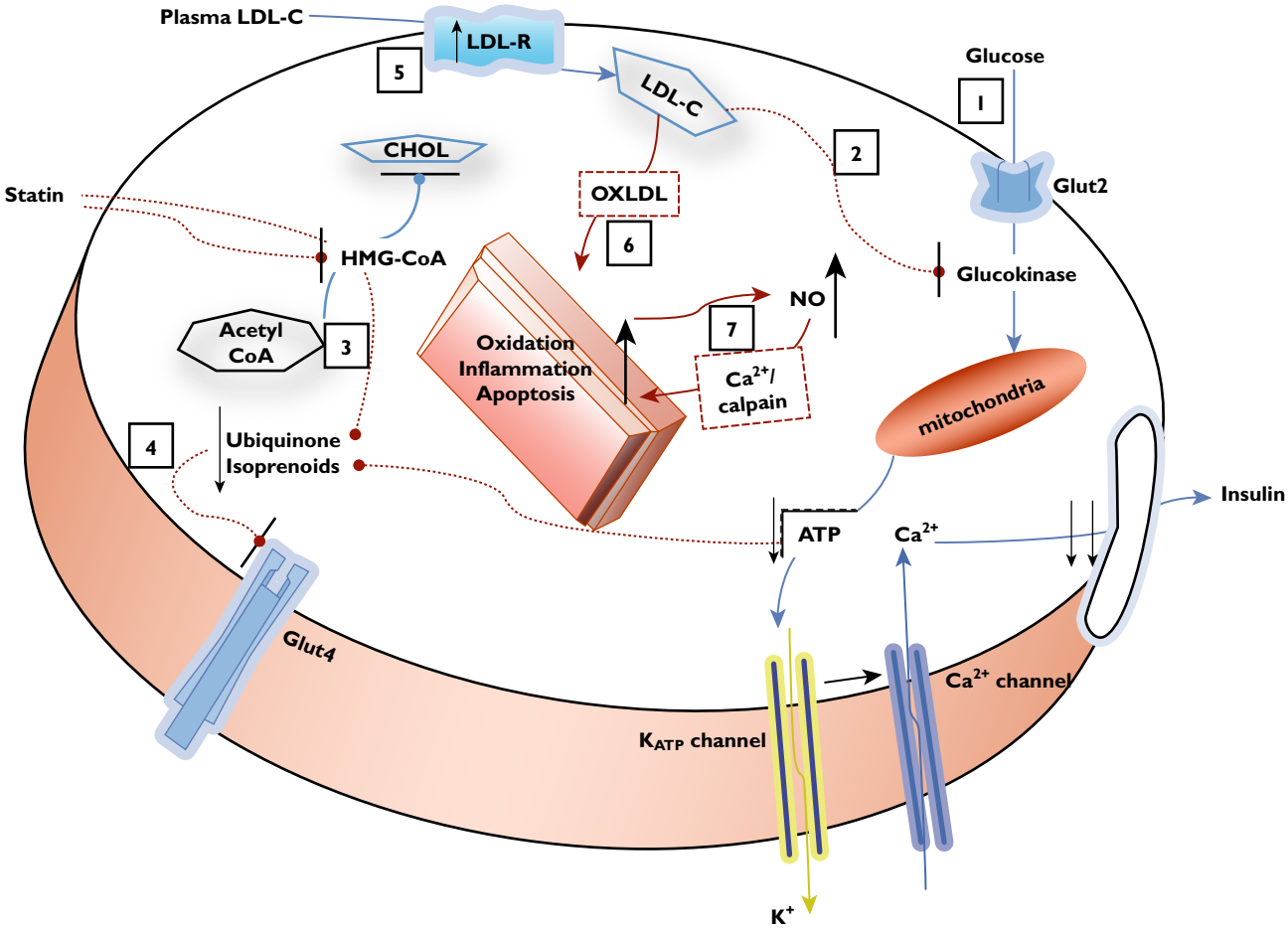

Figure 1

A paradigm for statin-induced dysregulation of glucose metabolism. (1) Intracellular arrival of glucose via glucose transporter (Glut 2 in beta cells) leads to phosphorylation by glucokinase and routing to the metabolic pathway. The resulting cascade of closure of ATP-dependent potassium channel, depolarization and calcium influx leads to insulin secretion; this process may be inhibited by statins [11, 12]. (2) Glucokinase is inhibited by abundance of plasma cholesterol [15], and thus is conceivably affected by statin-induced inhibition of *de novo* cholesterol synthesis with increased uptake of plasma LDL. (3) Statin inhibition of HMG-CoA reductase suppresses synthesis of ubiquinone (CoQ_{10}), an essential factor in the mitochondrial electron-transfer system, resulting in inhibition of insulin secretion due to reduced production of ATP. (4) Statin inhibition of HMG-CoA reductase suppresses the synthesis of isoprenoids, thus causing down regulation of Glut 4 expression on adipocyte cells leading to impaired glucose uptake. (5) The inhibition of HMG-CoA reductase causes upregulation of LDL receptors leading to enhanced uptake of LDL-cholesterol in an effort to replenish intracellular stores. However, the intracellular fate of plasma-derived LDL-cholesterol may be distinct from that of *de novo* synthesized cholesterol. (6) The oxidation of LDL-cholesterol may incite an inflammatory cascade that compromises the functional, e.g. insulin secretion apparatus, and ultimately structural integrity of the islet beta cells. (7) Furthermore, cytokine-induced over-production of nitric oxide (NO) has been shown to induce beta cell apoptosis via the activation of calpain, a calcium-dependent protease [16]. ATP, adenosine triphosphate; CHOL, cholesterol (*de novo* synthesized); Glut2, glucose transporter 2; Glut4, glucose transporter 4; HMG-CoA, 3-hydroxy-methylglutaryl coenzyme A; LDL, low density lipoprotein; LDL-C, low density lipoprotein cholesterol (plasma-derived); LDL-R, LDL receptor; OxLDL, oxidized LDL; NO, nitric oxide

(available on request from the corresponding author) and declare no support from any organization for the submitted work, SF had specified relationships with Merck, Roche, Kowa, Amarin, Novo, ISIS, Pfizer in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

Dr Sampson is supported in part by the Harold Amos Medical Faculty Development Award of the Robert Wood Johnson Foundation and Dr Jahangir is supported by National Institutes of Health Training Grant (T32 HL007411-32).

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RECEIVED
10 August 2012

ACCEPTED
17 August 2012

ACCEPTED ARTICLE PUBLISHED ONLINE
24 August 2012

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